Alaska Sentinel Surveillance Study of Helicobacter pylori Isolates from Alaska Native Persons from 2000 to 2008

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Helicobacter pylori infection is more common in Alaska Native persons than in the general U.S. population, with seroprevalence to H. pylori approaching 75%. Previous studies in Alaska have demonstrated elevated proportions of antimicrobial resistance among H. pylori isolates. We analyzed H. pylori data from the Centers for Disease Control and Prevention’s sentinel surveillance in Alaska from January 2000 to December 2008 to determine the proportion of culture-positive biopsy specimens with antimicrobial resistance from Alaska Native persons undergoing endoscopy. The aim of the present study was to monitor antimicrobial resistance of H. pylori isolates over time and by region in Alaska Native persons. Susceptibility testing of H. pylori isolates to metronidazole, clarithromycin, amoxicillin, and tetracycline was performed using agar dilution. Susceptibility testing for levofloxacin was performed by Etest. Overall, 45% (532/1,181) of persons undergoing upper endoscopy were culture positive for H. pylori. Metronidazole resistance was demonstrated in isolates from 222/531 (42%) persons, clarithromycin resistance in 159/531 (30%) persons, amoxicillin resistance in 10/531 (2%) persons, and levofloxacin resistance in 30/155 (19%) persons; no tetracycline resistance was documented. The prevalence of metronidazole, clarithromycin, and levofloxacin resistance varied by region. Female patients were more likely than male patients to demonstrate metronidazole (P < 0.05) and clarithromycin (P < 0.05) resistance. No substantial change in the proportion of persons with resistant isolates was observed over time. Resistance to metronidazole, clarithromycin, and levofloxacin is more common among H. pylori isolates from Alaska Native persons than those from elsewhere in the United States.

Helicobacter pylori is the major cause of gastric and duodenal ulcers and is associated with chronic active gastritis (27). Infected persons are at increased risk for mucosa-associated lymphoid tissue (MALT) lymphoma and gastric adenocarcinoma (2, 15). Over half of the world’s population is currently infected with H. pylori; rates of approximately 40% seropositivity have been found among persons living in industrialized countries, compared to 80 to 90% among persons living in developing countries (1, 7). In Alaska, the overall seroprevalence among Alaska Native persons is approximately 75% (range among regions, 64 to 81%) (23).

Previous studies have demonstrated elevated proportions of resistant H. pylori isolates from Alaska compared with the rest of the United States (7, 10, 12, 18, 21). We analyzed data from the Centers for Disease Control and Prevention’s (CDC) H. pylori sentinel surveillance system in Alaska from 1 January 2000 to 31 December 2008 to determine the proportion of H. pylori culture-positive biopsy specimens from Alaska Native persons undergoing upper endoscopy and to determine the susceptibility of H. pylori isolates to antibiotics (metronidazole, clarithromycin, levofloxacin, amoxicillin, and tetracycline) commonly used in the treatment of H. pylori infections in Alaska.

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TABLE 1. H. pylori antimicrobial susceptibility among isolates collected from Alaska Native persons between 1 January 2000 and 31 December 2008

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>% of patients (n = 1,181) who were H. pylori culture positive (no. positive/total no. of patients)</th>
<th>% of isolates that were resistant (no. resistant/total no. of isolates) to:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group (yr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30</td>
<td>41 (45/111)</td>
<td>27 (12/45) 22 (10) 2 (1) 4 (2) 14 (2/14) 15 (82) 19 (30/155)</td>
</tr>
<tr>
<td>30–40</td>
<td>50 (76/151)</td>
<td>54 (41/76) 29 (22) 1 (1) 20 (15) 14 (3/22)</td>
</tr>
<tr>
<td>40–50</td>
<td>52 (159/303)</td>
<td>43 (69/159) 32 (51) 0 (0) 16 (25) 24 (13/54)</td>
</tr>
<tr>
<td>50–60</td>
<td>42 (111/266)</td>
<td>49 (54/111) 30 (33) 4 (5) 22 (24) 18 (6/34)</td>
</tr>
<tr>
<td>60+</td>
<td>40 (140/350)</td>
<td>33 (46/140) 31 (43) 2 (3) 11 (16) 19 (6/31)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>46 (260/564)</td>
<td>52 (134/260) 37 (95) 3 (7) 21 (55) 24 (16/68)</td>
</tr>
<tr>
<td>Male</td>
<td>44 (271/617)</td>
<td>32 (88/271) 24 (64) 1 (3) 10 (27) 16 (14/87)</td>
</tr>
<tr>
<td>Region of residence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anchorage, AK</td>
<td>40 (175/442)</td>
<td>40 (70/175) 31 (54) 1 (2) 15 (27) 31 (16/52)</td>
</tr>
<tr>
<td>Bethel, AK</td>
<td>59 (175/297)</td>
<td>43 (76/175) 30 (52) 2 (4) 14 (24) 11 (2/19)</td>
</tr>
<tr>
<td>Dillingham, AK</td>
<td>38 (77/203)</td>
<td>40 (31/77) 27 (21) 0 (0) 16 (12) 14 (8/58)</td>
</tr>
<tr>
<td>Nome, AK</td>
<td>49 (54/110)</td>
<td>41 (22/54) 35 (19) 6 (3) 26 (14) 50 (3/6)</td>
</tr>
<tr>
<td>Other</td>
<td>38 (22/58)</td>
<td>40 (10/22) 41 (9) 5 (1) 23 (5) 10 (1/10)</td>
</tr>
<tr>
<td>Residence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urban</td>
<td>39 (135/343)</td>
<td>40 (54/135) 30 (41) 1 (1) 13 (18) 38 (15/9)</td>
</tr>
<tr>
<td>Rural</td>
<td>47 (396/838)</td>
<td>42 (168/396) 30 (118) 2 (9) 16 (64) 13 (15/11)</td>
</tr>
<tr>
<td>Medical facility</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANMC (Anchorage, AK)</td>
<td>41 (283/687)</td>
<td>44 (258/687) 31 (87) 1 (4) 16 (46) 24 (23/97)</td>
</tr>
<tr>
<td>YKDRH (Bethel, AK)</td>
<td>61 (143/236)</td>
<td>41 (59/143) 30 (43) 3 (4) 13 (18) 0 (0/6)</td>
</tr>
<tr>
<td>NSRH (Nome, AK)</td>
<td>54 (44/82)</td>
<td>36 (16/44) 32 (14) 5 (2) 20 (9)</td>
</tr>
<tr>
<td>Kanakanak Hospital (Dillingham, AK)</td>
<td>35 (61/176)</td>
<td>36 (22/61) 25 (15) 0 (2) 15 (9) 13 (7/52)</td>
</tr>
<tr>
<td>Avg (totals)</td>
<td>45 (531/1,181)</td>
<td>42 (222/531) 30 (159) 2 (10) 15 (82) 19 (30/155)</td>
</tr>
</tbody>
</table>

*The total number of isolates for this column is the same as the number listed in the metronidazole column. b P < 0.05. c P < 0.001; rates in the Yukon-Kuskokwim Delta were higher than in all other regions. d P = 0.002; Southcentral and Norton Sound regions versus all other regions. e P < 0.001; rates at the NSRH and YKDRH were higher than at the ANMC and Kanakanak Hospital.

(ii) *Susceptibility testing.* MIC testing was performed according to the guidelines of the Clinical and Laboratory Standards Institute (CLSI) (22) by agar dilution (as previously described (6)) from January 2000 through December 2008 for metronidazole, amoxicillin, clarithromycin, and tetracycline. MIC testing for levofloxacin by Etest started in August 2004 for all isolates.

(iii) *MIC breakpoints.* CLSI breakpoints were used to define resistance of *H. pylori* isolates to clarithromycin (MIC $\geq$ 1 $\mu$g/ml). The CLSI does not designate breakpoints for other antimicrobials used in the treatment of *H. pylori*. We used the following breakpoints for resistance, derived from prior studies: a metronidazole MIC of $>8$ $\mu$g/ml, an amoxicillin MIC of $\geq$1 $\mu$g/ml, a levofloxacin MIC of $\geq$2 $\mu$g/ml, a clarithromycin MIC of $\geq$1 $\mu$g/ml, and a tetracycline MIC of $\geq$2 $\mu$g/ml (7, 13).

**Statistical analysis.** Categorical and continuous variables were compared between groups using the chi-square and Kruskal-Wallis tests, respectively. Trends across age groups and study years were examined by the Cochran-Armitage test. Statistical analyses were conducted using SAS software version 9.2 (SAS Institute, Cary, NC). P values were two-tailed, and values of $<0.05$ were considered statistically significant.

**RESULTS**

A total of 1,799 specimens were obtained from 1,181 Alaska Native persons who underwent EGD. If persons underwent multiple EGDs in the same year, only the first EGD was used for this analysis ($n = 1,181$). Over the 9 years of surveillance, 58% ($n = 687$) of EGDs were done at the ANMC in Anchorage, 20% ($n = 236$) at the YKDRH in Bethel, 15% ($n = 176$) at Kanakanak Hospital in Dillingham, and 7% ($n = 82$) at the NSRH in Nome. The mean age of participants was 51 years (range, 3 to 96 years), and 52% ($n = 617$) were male.

Among 1,181 patients, 531 (45%) tested *H. pylori* culture positive. Among patients with *H. pylori*-positive cultures, the proportions of isolates demonstrating resistance to metronidazole, clarithromycin, levofloxacin, and amoxicillin were 42% (222/531), 30% (159/531), 19% (30/155), and 2% (10/531), respectively. No patients were infected with *H. pylori* isolates that demonstrated resistance to tetracycline (Table 1). CLO testing was performed on 80% ($n = 940$) of persons and was in concordance with culture results 86% ($n = 811$) of the time. Results of histologic evaluations of *H. pylori* presence were available for 78% ($n = 924$) of persons and were in agreement with the culture results 85% ($n = 781$) of the time. The performance of these and other tests for the
presence of *H. pylori* isolates in this population has been previously investigated (8).

The distributions of MIC values differed between the antimicrobials tested (Fig. 1). The distribution of amoxicillin MICs was unimodal, compared to the bimodal distributions of levofloxacin, clarithromycin, and metronidazole. For metronidazole, the MICs were distributed across the entire scale. Very few *H. pylori* isolates had MICs of levofloxacin and clarithromycin around the resistance cutoff, leading to a greater differentiation between resistant and susceptible strains.

**Metronidazole.** Overall, 42% (222/531) of *H. pylori* culture-positive patients had isolates resistant to metronidazole. Females were more likely to have metronidazole-resistant *H. pylori* isolates than males (52% [134/260] versus 32% [88/271], respectively; odds ratio [OR] = 2.6; \( P < 0.0001 \)) (Fig. 2). There was no statistically significant trend in the proportion of isolates demonstrating metronidazole resistance over the time period of the study; resistance varied by year from 30% to 51% of isolates (Fig. 3). Urban and rural areas had similar levels of metronidazole resistance at 40% (54/135) and 42% (168/396), respectively. The proportion of isolates demonstrating metronidazole resistance among referral hospitals was highest at the ANMC at 44% (185/283). Persons 30 to 40 years of age displayed the highest proportion of metronidazole-resistant isolates (54%), followed by the age groups of 50 to 60 years (49%) and 40 to 50 years (43%) (Table 1).

**Clarithromycin.** Overall, 30% (159/531) of persons were found to have *H. pylori* isolates resistant to clarithromycin. Females were more likely to have clarithromycin-resistant *H. pylori* isolates than males (37% [95/260] versus 24% [64/271],

*FIG. 1. MICs of commonly prescribed antibiotics for *H. pylori* isolates from Alaska Native persons, 2000 to 2008.*

*FIG. 2. Percentages of persons in Alaska with *H. pylori* isolates with antimicrobial resistance by patient sex, 2000 to 2008.*

of isolates resistant to levofloxacin varied by year from 10% to 31%; however, no statistically significant trend over the time period of the study was noted (Fig. 3). Five of the 10 patients infected with H. pylori isolates displaying resistance to amoxicillin were between the ages of 50 and 60 years, and 9 patients resided in rural areas; however, these results were not statistically significantly different (Table 1). There were no patients infected with H. pylori isolates resistant to tetracycline.

**DISCUSSION**

Data from four of five hospitals participating in the Alaska H. pylori sentinel surveillance network demonstrated a high proportion of culture positivity (45%) among EGD specimens obtained from Alaska Native persons over the 9-year surveillance period; persons living in the western region of Alaska had the highest proportion of culture positivity (59%). No distinct trends in antimicrobial resistance over time were seen; however, overall, the percentages of isolates demonstrating full resistance to metronidazole, clarithromycin, both metronidazole and clarithromycin, and levofloxacin were high (42, 30, 15, and 19%, respectively). Antimicrobial resistance was more commonly found among H. pylori isolates from Alaska Native persons than among those from persons elsewhere in the United States (12, 19, 21). Studies performed by Duck et al. (patients undergoing endoscopy at 11 different hospitals across the United States) (12) and Meyer et al. (meta-analysis of 20 H. pylori eradication trials across the United States) (21) demonstrated significantly lower proportions of isolates with resistance to clarithromycin or metronidazole than were found in Alaska Native persons. This is likely due to a higher endemicity of H. pylori infection in the Alaska Native population and to rates of antimicrobial prescription that are the same as or slightly higher than in the rest of the United States (4). To our knowledge, this long-standing H. pylori sentinel surveillance system for antimicrobial resistance is unique.

We found that the proportion of H. pylori isolates from Alaska Native persons demonstrating resistance to levofloxacin (19%) was at least twice as high as rates reported in Canada and countries in Western Europe (with the exception of Italy) (3, 9, 26) and comparable to rates reported in Jamaica and Korea (13, 16). No data are currently available on levofloxacin or quinolone resistance among H. pylori isolates from the United States, with the exception of Alaska. A study performed by Carothers et al. which looked at H. pylori isolates collected from 1998 to 2002 found that 8.8% of patients living in the urban setting of Anchorage, AK, who presented for EGD were infected with levofloxacin-resistant H. pylori isolates (10). Our surveillance data (which cover a later time period) show substantially higher overall levofloxacin resistance (19%) than in the study by Carothers et al. In our study, the proportion of isolates demonstrating levofloxacin resistance was approximately three times higher (P < 0.05) among persons residing in an urban (38%) than in a rural (13%) setting. The high proportion of levofloxacin resistance rates in Alaska could
be due to increased usage of fluoroquinolone antibiotics in the urban city of Anchorage. Due to the broad-spectrum coverage of levofloxacin and the ease of transition from intravenous to oral therapy, as well as the ease of oral, once-daily administration by patients, levofloxacin is prescribed frequently at the ANMC for respiratory and complicated urinary tract infections. Prescription of levofloxacin has occurred more frequently at the ANMC than in rural village clinics and may account for the significant difference in H. pylori resistance between the urban and rural areas (CDC, unpublished data).

A study by Bott et al. in Anchorage, AK, revealed that while overall prescription rates for fluoroquinolones were low, visit-based prescriptions for fluoroquinolones to persons 5 to 17 years of age increased from 1992 to 2004. An increase in rates of prescription of antimicrobials may contribute to the high rates of antimicrobial resistance (4).

We found that among Alaska Native persons, the proportion of clarithromycin-resistant H. pylori isolates (30%) was approximately three times higher, and the proportion of metronidazole-resistant isolates (42%) was two times higher, than in previous U.S. studies (12). These rates of resistance from Alaska are more consistent with rates found in developing countries. Our data support previous studies in Alaska and other parts of the world that demonstrate a high proportion of H. pylori isolates resistant to metronidazole and clarithromycin (6, 14, 18, 23, 24, 25). Neither metronidazole- nor clarithromycin-resistant isolates were associated with a particular age group or place of residence (urban versus rural).

An increase in the multidrug resistance of H. pylori isolates to commonly prescribed antibiotics has been previously documented (5, 6, 20, 28). In this study, persons infected with isolates resistant to metronidazole were more likely to have isolates resistant to clarithromycin as well. Additionally, persons infected with isolates resistant to metronidazole and clarithromycin were more likely to have isolates resistant to levofloxacin than persons infected with isolates susceptible to both antibiotics. Treatment for H. pylori in persons with H. pylori isolates resistant to multiple classes of antibiotics may result in higher treatment failure rates. Indeed, documented resistance to clarithromycin has been associated with higher treatment failure rates in Alaska and other parts of the world (17, 18).

Data from our study demonstrate that persons infected with H. pylori isolates resistant to three antimicrobial agents used to treat this infection (n = 10), metronidazole, clarithromycin, and levofloxacin, lived in both rural (n = 6) and urban (n = 4) Alaska. Due to a high proportion of H. pylori isolates demonstrating clarithromycin resistance, the most common treatment regimen used for H. pylori infection in Alaska has been quadruple therapy with metronidazole, tetracycline, omeprazole, and bismuth. Treatment regimens for H. pylori are selected from a limited formulary specific to the treatment facility. Medical providers are limited to the medications on a closed formulary when choosing a medication regimen. The high rates of prevalence of antibiotic-resistant H. pylori isolates, particularly those with multidrug resistance, in this population are of high concern.

We found that female subjects were more likely than males to be infected with isolates resistant to metronidazole and clarithromycin, as well as to both metronidazole and clarithromycin (Fig. 2). It has been shown in prior studies in Alaska and elsewhere that the increased resistance of H. pylori isolates in females may be due primarily to the increased prescription of metronidazole for gynecological infections (6, 11).

There were a number of limitations to this study. The findings may not be representative of the population of Alaska, as only Alaska Native people were included; the Alaska Native population is 20% of the population of the entire state of Alaska (U.S. Census, 2000). In addition, the Alaska sentinel surveillance sites do not cover the entire state of Alaska. Medical providers performing EGDs in the sentinel sites were not required to send in biopsy samples to the CDC for culture and susceptibility testing. Reliance on volunteer participation by physicians rather than mandatory reporting or delivery of a randomized sample may lead to a participation bias. Samples were analyzed based on culture testing. This sentinel surveillance for antimicrobial resistance did not collect information on endoscopic findings, such as duodenal ulcers, gastric ulcers, gastric cancer, gastric lymphoma, or nonulcer dyspepsia. We also did not have access to previous H. pylori treatment histories.

With the new findings and sustained high numbers of H. pylori isolates displaying antimicrobial resistance, continued surveillance in Alaska Native persons is warranted. The data from this surveillance system have been useful for informing empirical treatment of H. pylori infections in Alaska. Plans are in place for inclusion of these data in hospital antibiograms.

REFERENCES


